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1 **Unresectable Peritoneal Metastasis treated by Pressurized**
2 **Intraperitoneal Aerosol Chemotherapy (PIPAC) leading to**
3 **Cytoreductive Surgery And Hyperthermic Intraperitoneal**
4 **Chemotherapy.**

5

6 Mohammad Alyami, MD^{1,2,3}, Frederic Mercier MD, MSc^{1,4}, Matthieu Siebert MD^{1,2} ,
7 Pierre-Emmanuel Bonnot MD^{1,2} , Nathalie Laplace MD^{1,2} , Laurent Villeneuve,
8 PhD^{1,2}, Guillaume Passot MD, PhD^{1,2} , Olivier Glehen, MD, PhD^{1,2} , Naoual Bakrin,
9 MD, PhD^{1,2}, Vahan Kepenekian, MD^{1,2}

10 Department of General surgery & Surgical Oncology, Centre Hospitalier Lyon-Sud,
11 Hospices Civils de Lyon, Pierre-Bénite, France¹.

12 EMR 3738, Lyon 1 University, Lyon, France².

13 Department of General surgery and Surgical oncology, oncology Center, King Khalid
14 Hospital, Najran , Saudi Arabia³

15 Department of Surgical Oncology, Centre Hospitalo-Universitaire de Montreal,
16 Montreal, Canada⁴

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21 **Corresponding author:**

22 Mohammad ALYAMI, MD.

23 Department of General surgery & Surgical Oncology,

24 Centre Hospitalier Lyon-Sud,

25 165 Chemin du Grand Revoyet

26 69495, Pierre-Bénite

27 FRANCE

28 E-mail: swar_ms@hotmail.com

29 Tel: +33 4 78 86 13 77

30 Fax: +33 4 78 86 33 43

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33 **Running Head:** PIPAC before HIPEC

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35

36 **Key words:** Peritoneal carcinomatosis, unresectable PC (PM), PIPAC, CRS, HIPEC.

37

38 **Synopsis:**

39 PIPAC is a relatively new method of intraperitoneal chemotherapy treatment in

40 palliative set up, for unresectable peritoneal metastasis. Because of down staging,

41 selected patients may be offered secondary surgery.

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47 **ABSTRACT**

48 **Background:** PIPAC is a recent method of intraperitoneal chemotherapy. The aim of
49 this study was to describe the clinical characteristics of the patients who became
50 amenable to CRS & HIPEC after PIPAC treatment.

51

52 **Methods:** All patients diagnosed with unresectable PM who became resectable
53 throughout PIPAC treatment were included. Outcome criteria were adverse events
54 following PIPAC procedure and rate of secondary CRS and HIPEC.

55

56 **Results:** Four hundred thirty-seven PIPAC were done in 146 consecutive patients.
57 Among them, 26 patients (17.8 %) who underwent 76 PIPAC were scheduled for
58 CRS and HIPEC after reduction of the peritoneal burden. PM were from gastric,
59 peritoneal mesothelioma, ovarian, colorectal and small bowel in 13, 7, 4, 1 and 1
60 patients, respectively. At the time of the first PIPAC, median age was 58.6 years (32-
61 76.3). Median PCI was 16 (1-39). All patients had systemic chemotherapy in between
62 PIPAC session. Median consecutive PIPAC procedure was 3 (1-8). Complications
63 occurred in 3 PIPAC session (4%) and there was no major complication (CTCAE III
64 or higher). Complete CRS and HIPEC was achieved in 21 patients of the 26
65 scheduled (14.4%). The remaining 5 patients were considered unresectable at the
66 exploratory laparotomy. Among patients who underwent CRS and HIPEC, with
67 median follow-up of 7 (1-26) months, 14 patients (66.7%) were alive without
68 recurrence, 2 patients (9.5%) were alive with recurrence and 5 patients (23.8%) died.

69 **Conclusions:** Complete CRS and HIPEC can be achieved in strictly selected patient
70 with unresectable PM at diagnosis after repeated PIPAC session with palliative intent.

71

72 INTRODUCTION

73 Peritoneal metastasis (PM) is a common occurrence in intra-abdominal malignancies
74 and is associated usually with a dismal prognosis in the absence of an aggressive
75 therapeutic approaches (1). For unresectable PM, systemic chemotherapy remains the
76 gold-standard treatment even if its impact on survival is limited. With modern
77 association of chemotherapies and targeted therapies, expected median survival are
78 estimated at 16.3 months for colorectal cancer(2), 10.7 months for gastric cancer(3),
79 16.6 months for recurrent platin resistant ovarian cancer (4) and less than 12 months
80 for malignant peritoneal mesothelioma(5).

81 Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is relatively recent method
82 to deliver intraperitoneal chemotherapy. It seems to enhance the effect of
83 chemotherapy because of the physical properties of aerosol and pressure(6). PIPAC is
84 now a safe and tolerated technique that is well described(7-9). PIPAC techniques are
85 homogeneous throughout expert centers(10). Recently, PIPAC demonstrated
86 encouraging results in patients with unresectable PM(9, 11).

87 In the last 30 years, cytoreductive surgery (CRS) and hyperthermic intraperitoneal
88 chemotherapy (HIPEC) has become the cornerstone of resectable PM treatment. CRS
89 and HIPEC is the gold standard for pseudomyxoma peritonei and mesothelioma(12,
90 13) and an option for colorectal, ovarian and gastric PM in selected patients(14-16).

91 The aim of this study was to describe the clinical characteristics and extent of disease
92 of the patients who became resectable following PIPAC treatment and the preliminary
93 results of patients who underwent secondary CRS and HIPEC with a curative intent.

94

95 **METHODS**

96 **Study design**

97 A retrospective analysis from a single institutional PM database was conducted to
98 identify all patients who underwent PIPAC for unresectable PM between December
99 2015 and June 2018 and who were secondarily scheduled for CRS and HIPEC with a
100 curative intent (Figure 1). The study was performed in accordance with the precepts
101 established by the Declaration of Helsinki.

102 **Patient selection**

103 Every case was discussed at the multidisciplinary tumor board and the PIPAC or
104 secondary CRS and HIPEC indication was decided on an individual basis. PIPAC
105 were only considered in patients with unresectable disease who had an Eastern
106 Cooperative Oncology Group (ECOG) performance status of <2. Patients could be
107 considered unresectable because of the locoregional involvement of their primary
108 tumor or the extent of PM. Patients with intestinal obstruction, extra-peritoneal
109 metastases, or a history of severe hypersensitivity reactions to platinum or
110 doxorubicin compounds were not considered. Only patients who were amenable to
111 potential CRS and HIPEC were planned for exploratory laparotomy in HIPEC
112 conditions. For those patients, the following data were collected: gender, age at the
113 time of first PIPAC, origin of PM, history of chemotherapy before PIPAC, extent of
114 PM determined by the Peritoneal Cancer Index (PCI)(17) using peritoneal malignancy
115 Stage Evaluation (PROMISE) application(18), delay between PIPAC and systemic
116 chemotherapy. PCI at CRS, surgery length, chemotherapy used for HIPEC, length of
117 hospital stay, morbidity and mortality. Adverse events were assessed according to the
118 Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

119 **PIPAC surgical technique**

120 Under general anesthesia, a balloon trocar (Applied Medical, Paris, France) was
121 placed in the midline, using the open access laparoscopic technique, and a
122 capnoperitoneum of 12 mmHg at 37°C was applied. Another balloon trocar was
123 placed in the midline under direct visualization. Explorative laparoscopy was
124 performed, and the PCI was calculated. Parietal biopsies were performed, ascites was
125 aspirated, measured and sent for peritoneal cytology. A nebulizer CAPNOPEN®
126 (Reger Medizintechnik, GmbH, Villingendorf, Germany) was then connected to a
127 high-pressure injector and inserted into the abdomen through one of the trocar. The
128 safety protocol with a standardized checklist containing all safety items was
129 systematically used before administration of cytotoxic, as described previously(19-
130 22). A pressurized aerosol containing chemotherapy agents was then applied. The
131 chemotherapies administrated were cisplatin (7.5 mg/m² body surface in 150 ml NaCl
132 0.9%) immediately followed by doxorubicin (1.5 mg/m² in 50 ml NaCl 0.9%), or
133 oxaliplatin (92 mg/m² in 150 mL NaCl 0.9%). The choice was based principally on
134 PM origin and previous history of chemotherapy. The system was then kept for 30
135 minutes (application time). Remaining aerosol was exhausted using a closed surgical
136 smoke evacuation system. Trocars were removed and anti-adhesive gel was applied.
137 Aponeurosis and skin were then closed. PIPAC was aimed to be repeated every 6 to 8
138 weeks for at least three procedures. If PM was considered resectable during the
139 laparoscopic exploration of a PIPAC, patients were planned for exploratory
140 laparotomy with a possible CRS and HIPEC during the same surgery.

141

142

143 **Technique of CRS and HIPEC**

144 CRS was performed with a specific team of surgeons, anesthesiologists, and nurses
145 dedicated and experienced in this procedure. Following laparotomy, PCI was assessed
146 using the PCI. Cytoreductive surgery was performed with the goal of achieving
147 complete excision of macroscopic disease by a combination of peritonectomies and
148 organ resection, as described by Sugarbaker(23). The quality of the CRS was defined
149 according to the Sugarbaker completeness of cytoreduction (CC) score: CC-0, no
150 macroscopic residual tumor; CC-1, residual tumor <2.5 mm; CC-2, residual tumor
151 between 2.5 mm and 25 mm; CC-3, residual tumor >25 mm(24).

152 Following CRS, HIPEC was performed by circulating a heated solvent infused with
153 chemotherapeutic agent throughout the abdomen. This was performed using closed
154 technique. The choice of cytotoxic agent and duration of hyperthermia depended on
155 the origin of PM. The HIPEC protocols used included monotherapy of cisplatin,
156 mitomycin C and oxaliplatin or combination of cisplatin and doxorubicin, as
157 previously reported(25-29).

158 **Statistical analysis**

159 Descriptive results were presented as a number (percentage) for qualitative variables
160 and as a mean \pm standard deviation (SD) or median (minimum-maximum) for
161 quantitative variables.

162

163

164

165 **RESULTS**

166 Four hundred thirty seven PIPAC procedures were done in 146 consecutive patients
167 between December 2015 and June 2018 (Table 1). Among them, 26 patients (17.8 %)
168 who underwent 76 PIPAC were then scheduled for exploratory laparotomy and
169 possible CRS and HIPEC. PM was from several different primary: gastric, malignant
170 mesothelioma, ovarian, colorectal and small bowel cancer in 13, 7, 4, 1 and 1 patients,
171 respectively. Nineteen patients (73%) were female. Median age at the first PIPAC
172 session was 58.6 years (32-76.3). Median PCI was 16 (1-39). Seven (26.9%) patients
173 had been treated with more than 2 lines chemotherapy before surgery. All patients
174 received systemic chemotherapy between PIPAC treatments. Median consecutive
175 PIPAC procedure was 3 (1-8). Median hospital stay after a PIPAC procedure was 3
176 days (2-5). Complications occurred in 3 PIPAC (4%) and there was no major
177 complication (CTCAE III or higher).

178 Twenty-six patients were brought to the operation room for a potential CRS and
179 HIPEC (17.8%). Complete cytoreduction (CC-0 or CC-1) was achieved in 21 patients
180 (14.4%) (Table2). The remaining 5 patients had exploratory laparotomy, which found
181 unresectability criteria. Median PCI during CRS and HIPEC was 12. Major
182 complications (CTCAE III, IV) (Table 3) occurred for 11 patients (52.3%). One
183 patient died (4.7%) in post-operative period because of bowel ischemia. Median
184 hospital stay was 15 days (7-58). The median follow-up was 7 (1-26) months. Among
185 patients who underwent CRS and HIPEC, 14 (66.7%) are alive without recurrence, 2
186 (9.5%) are alive with recurrence and 5 (23.8%) died. Details of the follow-up and the
187 current status are summarized in Table 4.

188

189 **DISCUSSION**

190 Our study suggests that, with an appropriate patient selection, CRS and HIPEC could
191 be proposed for some patients with unresectable PM after neoadjuvant PIPAC
192 treatments. In our study, 14.4% of patients were eligible to a secondary CRS and
193 HIPEC after being considered unresectable prior to PIPAC treatments and treated
194 with a palliative intent.

195 Secondary CRS and HIPEC after PIPAC was first described by Girshally et al(30).
196 They performed CRS and HIPEC in 21 patients out of 406 (5.2 %) with unresectable
197 PM. Among those 5.2% of patients, more than 50% of them were with low PCI
198 (mean 5.8 ± 5.6). In our study, 14.4 % of patients with initial median PCI of 16 had a
199 successful secondary CRS and HIPEC. Exploratory laparotomy and possible
200 CRS/HIPEC was offered to two patients after the first PIPAC session since they had
201 limited and resectable PM at the laparoscopic exploration. These two patients had no
202 PIPAC indication and could have been probably planned for an upfront CRS and
203 HIPEC. The first patient had his surgical exploration in another center, while the
204 second patient unresectability was assessed by CT scan evaluation. Girshally et al(30)
205 suggested that the mean number of PIPAC treatments necessary to convert diffuse
206 intraperitoneal metastasis into localized disease was close to four, in a time period of
207 4.5 to 6 months. In our series, the median number of PIPAC treatments to achieve
208 complete CRS and HIPEC was 3.

209

210 Multiple studies showed that about 75% of patients with unresectable PM develop
211 major or complete intraperitoneal tumor regression assessed by histology, after
212 repeated PIPAC treatment (31-33). In our experience, indication for CRS and HIPEC

213 were based on macroscopic and radiological responses principally. Histological
214 response was mainly used as an indicator of chemotherapy sensitivity. The
215 histological evaluation of tumor response represents an important issue. For now, it
216 should be interpreted with caution because there is great heterogeneity in peritoneal
217 distribution of disease and no standardization in biopsies location. It still needs to be
218 validated in prospective study. Many patients were not primary candidate for CRS
219 and HIPEC principally due to diffuse small bowel involvement. That is why a strict
220 selection of patients for CRS/HIPEC is very important and should always be based on
221 macroscopic, radiological and pathological findings. To avoid “open and close”
222 procedures that occurred for 5 of the 26 patients selected for a curative procedure,
223 laparoscopic evaluation requires careful and extensive evaluation of potential
224 contraindication of complete CRS. We recommend the use of monotrocar and
225 palpation combined to visualization of the entire small bowel. It may require also
226 more than the 4 samples usually required for the evaluation of pathologic
227 response(34).

228 The mortality rate of PIPAC procedure described in the literature is up to 8.3%(33).
229 Morbidity rate is quite variable with major complications occurring in 0 to 37% of
230 patients(7). In our study the overall complication was 4 % without any mortality post
231 PIPAC giving better result than what we previously published (11), suggesting a
232 better selection of patients or a learning curve effect. We reported 52.3% of major
233 complication (CTCAE III, IV) following secondary CRS and HIPEC. This
234 corresponds to a high rate of major complication when compared to literature but it
235 correlate to previous reports about HIPEC procedure in our center, where
236 complications were prospectively recorded and included 90-days morbidity (35, 36).

237 Our follow-up was too short to advance any conclusions on long-term results but few
238 patients already had prolonged survival (Table 4) whereas they presented an
239 unresectable disease with poor short-term prognosis. Undoubtedly, some of them who
240 died from an early recurrence did not have any benefit from such aggressive
241 procedure and would had probably longer survival with continuous combined
242 intravenous and PIPAC treatments. On the other hand, some of our patients have
243 prolonged disease-free survival such 21, 26, 22 and 18 months for some patients with
244 gastric, malignant mesothelioma, ovarian and small bowel PM respectively. We will
245 have to identify prognostic factors to better select the best candidate for these
246 aggressive procedures.

247 This study has limitations. First, its retrospective nature and multiples selection bias
248 that may affect patients who were scheduled for CRS/HIPEC. Second, patient
249 population was heterogeneous regarding origin of PM, number of preoperative
250 chemotherapy lines and the tumor chemo-sensitivity. . Third, quality of life evaluation
251 was not performed. This is related to the absence of long-term follow-up. However,
252 this series demonstrated the possibility of tumor regression induced by neoadjuvant
253 PIPAC associated to systemic chemotherapy in a palliative intent; leading to CRS and
254 HIPEC

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260 **CONCLUSION:**

261 Secondary CRS and HIPEC might become possible after repeated PIPAC treatments
262 combined to systemic chemotherapy for highly selected patient. Prospective studies
263 are mandatory to determine the role of PIPAC as a neoadjuvant therapy for patient
264 with unresectable PM.

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266

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423 better describe post-operative outcome after cytoreductive surgery and hyperthermic
424 intraperitoneal chemotherapy. *International Journal of Hyperthermia*. 2017.

Figure 1: Flow diagram of patients who were scheduled for CRS and HIPEC.

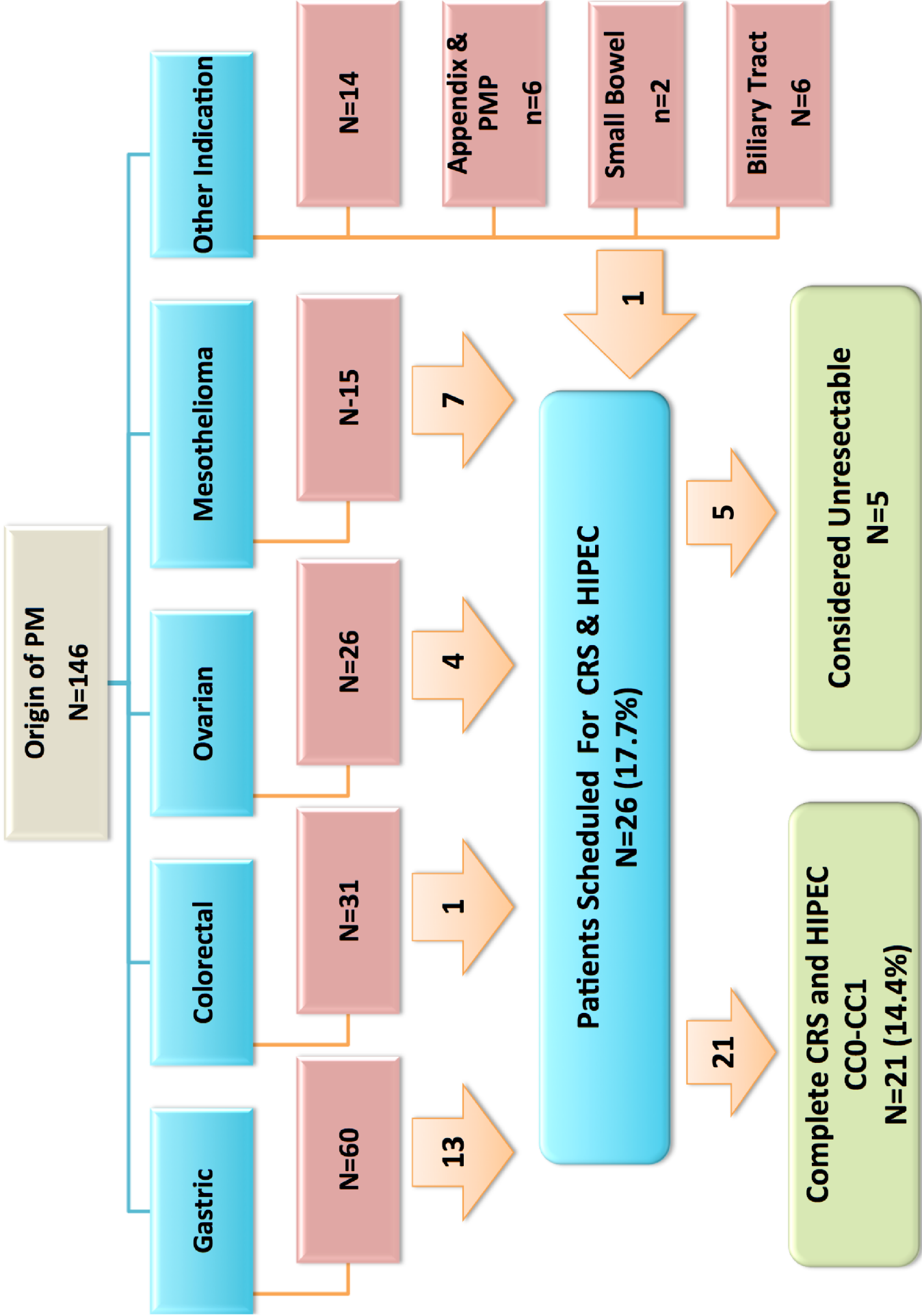


Table 1: Clinicopathological data for patients treated with PIPAC before CRS and HIPEC ^a.

Variable	Value N	Percentage
Total number of patients	146	
Total number of PIPAC	437	
Number of patients scheduled for CRS and HIPEC	26	17.8
Total number of PIPAC in patients scheduled for CRS and HIPEC	76	17.4
Sex (M: F)	7:19	30:70
Age, median years (range)	58.6 (32-76.3)	
Origin of PC		
Gastric	13	50
Mesothelioma	7	26.9
Ovarian	4	15.3
Colon	1	3.8
Small bowel	1	3.8
Preoperative Chemotherapy		
1 line	26	100
2 lines	7	26.9
Systemic chemotherapy associated with PIPAC	26	100
PCI median at time of first PIPAC	16 (1-39)	
Median consecutive PIPAC procedure	3 (1-8)	
Median hospital stay after a PIPAC procedure	3 (2-5)	
Overall complication (PIPAC)	3	4
Major complication of PIPAC (CTCAE III, IV)	0	0

^a Values in table are numbers of patients (percentages) unless otherwise indicated.

Table 2: Operative data and post-operative outcome for patients scheduled for CRS and HIPEC ^a.

Variable	Value N	Percentage
Patients scheduled for CRS and HIPEC	26	17.8
PCI median at time of CRS and HIPEC	12 (1-30)	
Completeness of cytoreduction (CC) score		
CC-0	13	
CC-1	8	
CC-3	5	
Optimal CRS and HIPEC (CC0, CC1)	21	14.4
Unresectable patients (no HIPEC)	5	
Cause of unresectability		
Extensive small bowel serosal involvement	2	
Extensive involvement of diaphragm	1	
Extensive involvement of liver hilum	1	
Extensive involvement of esophagus	1	
Median hospital stay (Day)	15 (7-58)	
Median follow-up of patients after CRS and HIPEC (Month)	7 (1-26)	
Alive without recurrence	14	66.7
Alive with recurrence	2	9.5
Died	5	23.8

^a Values in table are numbers of patients (percentages) unless otherwise indicated.

Table 3: Postoperative morbidity and mortality after CRS & HIPEC.^a

Variable	Value N (%) 21 Patients
Death within 90-days	1 (4.7)
Surgical complications	5 (23.8)
Intraabdominal abscess	1 (4.7)
Intraabdominal bleeding	2 (9.5)
Wound infection	2(9.5)
Medical complications	9(42.8)
Hematologic	5(23.8)
Hemoglobin <80g/L (4.9mmol/L)	
Hemoglobin<65g/L (4mmol/L)	
Neutrophil granulocytes < 1,000/mm ³	
Associated with hyperthermia (>38.5)	
Platelet <50,000/mm ³	
Cardiovascular	1 (4.7)
Cardiac arrhythmia	
Digestive arterial thrombosis	
Deep venous thrombosis or pulmonary embolism	
Gastrointestinal	5(23.8)
Anorexia needing parenteral alimentation	
Pancreatitis	
Respiratory	0(0)
Acute respiratory distress syndrome	
Renal	5(23.8)
Renal insufficiency needing dialysis	1(4.7)
At least one complication	11 (52.3)
More than one complication	5 (23.8)

Treatment	Interventional radiology	0 (0)
	Endoscopic	0 (0)
	Surgery	3 (14.3)

^a Values in table are numbers of patients (percentages) unless otherwise indicated.

Table 4: Follow-up for patients after Cytoreductive surgery and HIPEC

Patient	Primary Malignancy	CC score	HIPEC drug used	Follow up (Month)	Status (Dead, Alive with recurrence, Alive free of disease)	Site of recurrence (comment)
1	Gastric	1	Mitomycin C	5	Dead	Peritoneal
2	Gastric	0	Mitomycin C	18	Alive with recurrence	Peritoneal / Bone
3	Gastric	0	Cisplatine	6	Dead	Peritoneal
4	Gastric	0	Oxaliplatin	21	Alive free of disease	N/A
5	Gastric	0	Mitomycin C	14	Alive with recurrence	Breast
6	Gastric	0	Cisplatine	9	Alive free of disease	N/A
7	Gastric	0	Cisplatine	7	Alive free of disease	N/A
8	Gastric	0	Cisplatine	9	Alive free of disease	N/A
9	Gastric	0	Mitomycin C	1	Dead	(Bowel ischemia)
10	Gastric	0	Cisplatin+Doxo	7	Alive free of disease	N/A
11	Malignant mesothelioma	1	Cisplatin+Doxo	26	Alive free of disease	N/A
12	Malignant mesothelioma	1	Cisplatin+Doxo	25	Alive free of disease	N/A
13	Malignant mesothelioma	1	Cisplatin+Doxo	5	Dead	Pleura
14	Malignant mesothelioma	1	Cisplatin+Doxo	9	Dead	Peritoneal
15	Malignant mesothelioma	1	Cisplatin+Doxo	4	Alive free of disease	N/A
16	Malignant mesothelioma	0	Cisplatin+Doxo	6	Alive free of disease	N/A

17	Ovarian	0	Cisplatine	22	Alive free of disease	N/A
18	Ovarian	0	Cisplatin+Doxo	7	Alive free of disease	N/A
19	Ovarian	1	Cisplatin+Doxo	6	Alive free of disease	N/A
20	Ovarian	1	Cisplatine	3	Alive free of disease	N/A
21	Small bowel	0	Mitomycin C	18	Alive free of disease	N/A

* CC Score: Completeness of cytoreduction score.

** Doxo: Doxorubicin

*** N/A: Not applicable